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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,355	HARIRI ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-9,12-14,16,25,26,28-30,32,33,46-49 and 102-120* is/are pending in the application.

4a) Of the above claim(s) *46-49 and 105-120* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-9,12-14,16,25,26,28-30,32,33 and 102-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/15/07 has been entered.

Election/Restrictions

Applicant's request to rejoin claims 5, 12, 28, and 46-49 has been considered, and the examiner agrees in part. Claims 5, 12, and 28 ONLY are rejoined to the elected claims. Claims 46-49 differ in scope from elected claim 1, which is drawn to a method of modulating the differentiation of HSC into a blood cell. Claim 46 is far broader.

Newly submitted claims 105-120 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: They are drawn to a method of modulating proliferation of hematopoietic stem cells and, therefore, would have been placed into non-elected Group II in the restriction mailed 6/10/05 had they been presented originally.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 105-120 are withdrawn from

consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Response to Amendments

Applicant's amendments filed 6/15/07 to claims 1, 16, and 25 have been entered. Claims 2 and 11 have been cancelled in this amendment and claims 3, 4, 10, 15, 17-24, 27, 31, 34-45, and 50-101 were canceled in previous amendments. Claims 103-120 have been added. Claims 1, 5-9, 12-14, 16, 25, 26, 28-30, 32, 33, 46-49, and 102-120 remain pending in the current application, of which claims 1, 5-9, 12-14, 16, 25, 26, 28-30, 32, 33, and 102-104 are being considered on their merits. Claims 46-49 and 105-120 are withdrawn from consideration at this time. Prior art references not included with this Office action can be found in a prior action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 104 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of modulating some aspects of proliferation and differentiation of mammalian stem or progenitor cells to varying degrees using a few PDE4 inhibitors, does not reasonably provide enablement for methods of inducing specific differentiation end points (including the production of hematopoietic cells) comprising treating any given mammalian stem or progenitor cell with any given PDE4 inhibitor. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

Claim 104 requires that hematopoietic stem or progenitor cells (HSCs) be treated with a compound having Formula VII at page 43, line 5, of the specification ("Formula VII"), or one of its analogues, to yield a cell that expresses a particular combination of differentiation markers.

Directing the differentiation or proliferation of HSCs to a particular end is a major problem in the stem cell art, despite the relatively high level of ordinary skill therein. Eckfeldt et al. (2005, *PLoS Biology* 3: 1449-1458) teach that even years after time of the claimed invention, methods for regulating the differentiation and proliferation of HSCs *in vitro* are nascent and not well understood (page 1449, column 1). Eckfeldt et al. also teach that one fraction of bone marrow HSCs are $CD34^{+}CD33^{-}CD38^{-}$ when they are collected from the marrow; however, the specification and art provide no guidance for treating $CD34^{+}CD33^{-}CD38^{-}$ cells to produce $CD34^{+}CD33^{+}CD38^{-}$ cells, as in claim 104.

CD33 is a marker of monocytes and macrophages, not HSCs (see http://www.cancerindex.org/geneweb/CD33.htm). In light of the unpredictable nature of the stem cell differentiation art and the breadth of the claims, the specification fails to provide sufficient guidance for treating HSCs with Formula VII to yield cells that express the monocyte marker CD33.

This rejection was previously made over now-canceled claim 11 and is now applied over new claim 104, which includes the non-enabled embodiments of claim 11. Regarding the rejection of record, applicants allege that Example 11 teaches how to facilitate the modulation of differentiation of $CD34^+CD33^-CD38^-$ stem cells to produce $CD34^+CD33^+CD38^-$ cells (Reply, page 8, paragraph 2). Applicant alleges that the examiner indicated that identifying the proper amount of the compound would have been routine *(ibid.)*. These arguments have been fully considered, but they are not persuasive.

As discussed in the advisory action mailed 1/29/07, Example 11 is prophetic, and no experimental data was provided in the specification regarding the differentiation of stem cells which do not express CD33 to cells that do express CD33. If little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004): "Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no

knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology" (citations omitted). See M.P.E.P. § 2164.03. Applicant has not provided a specific and useful teaching other than the wish or plan for the method of claim 104 as described in Example 11; prophetic examples cannot enable nascent technology.

Regarding routine optimization, the comment pointed out by applicant was applied to the embodiment of canceled claim 11 in which the stem cells express CD33.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7-9, 16, 25, 26, 29, 30, 32, 33, 102, and 103 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gaspar Elsas et al. (2000, *British Journal of Pharmacology* 130: 1362-1368) taken in view of Muller et al. (2000, U.S. Patent 6,020,358) and Janowska-Wieczorek et al. (2001, *Blood* 98: 3143-3149). The claims are drawn to a method for modulating the proliferation or differentiation of a mammalian

hematopoietic stem or progenitor cell comprising contacting said cell with a compound having Formula VII at page 43, line 5, of the specification ("Formula VII"), or one of its analogues; and a composition that may be made thereby. In some dependent claims, the compound is present in a particular concentration; in some dependent claims, the cell is human. In some dependent claims, the cells are CD34+ or $CD11b^+$ cells.

Gaspar Elsas teach isolating mouse bone marrow, which comprises CD34+ and $CD11b^+$ hematopoietic stem cells (HSCs; see abstract of Janowska-Wieczorek), and treating the same with rolipram, a PDE4 inhibitor (page 1363, column 2, paragraph 2; table 1). Treating the cells of Gaspar Elsas with rolipram affects the degree of colony formation by said cells (Table 1), which is an indicator of differentiation. The cell culture dish of Gaspar Elsas is a "subject" according to the broadest reasonable definition of the term (*i.e.*, "that which experiences or is subjected to a treatment").

Gaspar Elsas et al. does do not teach contacting HSCs with Formula VII, or contacting human HSCs with any PDE IV inhibitor. Gaspar Elsas does not teach the concentrations recited in claim 7, for example.

Muller teaches phenethylsulfone compounds that decrease TNFα levels and inhibit PDE4 (column 4, lines 29-32). In particular, one of the claimed embodiments of the compound of Muller corresponds to Formula VII. Referring to column 5, lines 1-44, Formula VII is identical to Formula I of Muller, wherein Y is C=O; R^1, R^2, and R^3 and hydrogen; R^4 is $-NR^8R^9$; R^5 is alkoxy of 1 carbon atom; R^6 is alkoxy of 2 carbon atoms; R^7 is alkyl of 1 carbon atom; one of R^8 and R^9 is hydrogen and the other is $-COR^{10}$; and R^{10} is alkyl of 1 carbon atom (see also claim 1), *i.e.*, 2-[1-(3-ethoxy-4-

methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione (Abstract; hereafter "the compound of Muller").

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the compound of Muller et al. into the method of Gaspar Elsas et al. because both rolipram and the compound of Muller are PDE4 inhibitors. The skilled artisan would have been motivated to make such a substitution because Muller teach that the compound of Muller and the other compounds disclosed therein are useful in increasing cyclic AMP levels in cells (column 4, lines 28-53).

The selection of the amount of the compound of Muller to add to the HSCs in the method of Gaspar Elsas would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Gaspar Elsas teach varying the amount of PDE4 inhibitor added to the cells (Table 1). A holding of obviousness over the cited claims is therefore clearly required.

The selection of mammal from which to obtain HSCs would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Gaspar Elsas teaches that murine and human bone marrow have similar properties (page 1362, column 2). A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute varying amounts of the compound of Muller for the varying amounts of rolipram and in the method of Gaspar Elsas because the compounds are functional equivalents, and because the amount of compound would

have constituted routine optimization at the time of the invention. Furthermore, substituting human HSCs for murine HSCs would have been obvious, because Gaspar Elsas teach that both humans and mice are mammals with bone marrow having similar properties.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicants allege that the prior art does not suggest substituting the compound of Muller for the rolipram of Gaspar Elsas for modulating differentiation (Reply, page 9, paragraph 3). Applicants allege that Gaspar Elsas teaches the effect of rolipram on cyclic AMP levels, not differentiation *(ibid.)*. Applicants allege that the action of PDE4 inhibitors is unpredictable *(ibid.* and page 10, paragraph 2*)*. These arguments have been fully considered, but they are not persuasive.

In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court determined that motivation to combine prior art references need not be explicitly stated in the cited prior art; rather, the Court reiterated the standard set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 [148 USPQ 459], which required determining the scope of the prior art, ascertaining differences between the prior art and the instant claims; and resolving the level of ordinary skill in the pertinent art to determine the obviousness or nonobviousness of the claimed invention. In *KSR*, the Court reiterated the standard for overcoming obviousness rejections initially set forth in *Graham v. Deere*, namely convincing arguments that the cited art is non-analogous, a showing that the prior art teaches away from the claimed invention, or a showing of

secondary considerations, *e.g.* truly unexpected results (see *KSR* at 1399). "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103" (see *KSR* at 1397).

In this case, Gaspar Elsas teaches that contacting hematopoietic stem cells with rolipram, a PDE4 inhibitor, inhibits the action of PDE4, thereby raising the cAMP levels within the cells and effecting differentiation to mature GM-CSF-stimulated colonies (Abstract; page 1363, column 2, paragraph 1; Table 1 at page 1364). Gaspar Elsas recognized the link between cAMP levels in HSCs and progression of hematopoiesis (page 1366, column 2, first paragraph under "Discussion"). In summary, Gaspar Elsas teaches that raising cAMP levels in HSCs by way of PDE4 inhibition leads to hematopoietic differentiation. Muller teaches that the compound of Muller, like the rolipram of Gaspar Elsas, is a PDE4 inhibitor. Therefore, at the time of the invention, skilled artisans were aware of a link between PDE4 inhibition in HSCs and hematopoietic differentiation, and they were aware of numerous PDE4 inhibitors, including rolipram and the compound of Muller. Because Gaspar Elsas teaches that PDE4 inhibition leads to hematopoietic differentiation, the choice of PDE4 inhibitor would have constituted routine optimization for the person of ordinary skill in the art for the reasons set forth within the rejection.

Applicants' comments about the unpredictability of the action of PDE4 inhibitors on HSCs are not supported by evidence or declaration. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration. Muller teaches that the compound of Muller increases cAMP levels by inhibiting PDE4 (column 4, lines 29-36), and Muller recognized an effect of cAMP levels on blood cells (column 4, lines 4-9). Therefore, since the rolipram of Gaspar Elsas and the compound of Muller both increase cAMP levels by inhibiting PDE4, they are art-accepted equivalents absent a substantive evidentiary showing to the contrary.

Claims 6, 13, 14, and 104 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gaspar Elsas taken in view of Muller and Janowska-Wieczorek as applied to claims 1, 7-9, 16, 25, 26, 29, 30, 32, 33, 102, and 103 above, and further in view of Waki et al. (1999, *Japan Journal of Pharmacology* 79:477-483). The claims are drawn to methods and compositions as described above. In some dependent claims, the contacting is conducted *in vivo*.

The teachings of Gaspar Elsas, Muller, and Janowska-Wieczorek are relied upon as discussed above.

Gaspar Elsas, Muller, and Janowska-Wieczorek do not teach contacting HSCs with a PDE4 inhibitor *in vivo*.

Waki et al. teach administering 1-*n*-butyl-3-*n*-propylxanthine (XT-44), a PDE4 inhibitor, subcutaneously or orally to rats (page 478, column 2, through page 479, column 1; Figures 2-4).

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the compound of Muller for the XT-44 of Waki because both are phosphodiesterase inhibitors. The skilled artisan would have been motivated to make such a substitution because Muller contemplates administering the compound of Muller for treatment of various conditions (column 4, lines 35-54).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute the compound of Muller for the XT-44 of Waki et al. because the two are functional equivalents.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicants rely in part on arguments traversing the above rejection to traverse this rejection (Reply, page 11, paragraph 1). Additionally, applicants allege that Muller did not recognize the effects of their compounds for the modulation of differentiation of stem cells (Reply, page 11, paragraph 2). These arguments have been fully considered, but they are not persuasive.

Regarding the arguments set forth against this rejection that also traverse the rejection of claims 1, 7-9, 16, 25, 26, 29, 30, 32, 33, 102, and 103 over Gaspar Elsas, Muller, and Janowska-Wieczorek, the response set forth above to arguments also applies to this rejection.

As discussed above, Muller established that the compound of Muller increases cAMP levels by inhibiting PDE4, and Gaspar Elsas recognized a link between PDE4 inhibition and hematopoietic differentiation. Furthermore, Muller identified an effect of the compound of Muller on blood cells. Therefore, at the time of the invention, the prior art as a whole would have concluded that applying a PDE4 inhibitor to blood cells would modulate hematopoietic differentiation; the choice of PDE4 inhibitor would have been a matter of routine optimization, absent some evidentiary showing to the contrary.

Claims 1, 6-9, 13, 14, 16, 25, 26, 29, 30, 32, 33, and 102-104 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Waki taken in view of Muller. and Janowska-Wieczorek et al. The claims are drawn to methods as discussed above.

Waki teaches isolating rat bone marrow, which comprises CD34+ and $CD11b^{+}$ hematopoietic stem cells (HSCs; see abstract of Janowska-Wieczorek), and treating the same with 1-*n*-butyl-3-*n*-propylxanthine (XT-44), a PDE4 inhibitor (page 478, column 2; Figure 1). Waki also teaches administering XT-44 subcutaneously or orally to rats (page 478, column 2, through page 479, column 1; Figures 2-4).

Waki does not teach contacting cells with Formula VII, the compound of Muller.

Muller et al. teach phenethylsulfone compounds that decrease TNFα levels and inhibit PDE4 (column 4, lines 29-32). In particular, one of the claimed embodiments of the compound of Muller et al. corresponds to Formula VII. Referring to column 5, lines 1-44, Formula VII is identical to Formula I of Muller et al., wherein Y is C=O; R^1, R^2, and R^3 and hydrogen; R^4 is $-NR^8R^9$; R^5 is alkoxy of 1 carbon atom; R^6 is alkoxy of 2 carbon atoms; R^7 is alkyl of 1 carbon atom; one of R^8 and R^9 is hydrogen and the other is $-COR^{10}$; and R^{10} is alkyl of 1 carbon atom (see also claim 1), *i.e.*, 2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-aminoisoindoline-1,3-dione (Abstract; "the compound of Muller").

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the compound of Muller into the method of Waki because both XT-44 and the compound of Muller are PDE4 inhibitors. The skilled artisan would have been motivated to make such a substitution because Muller et al. teach that the compound of Muller and the other compounds of the invention are useful in increasing cyclic AMP levels in cells (column 4, lines 28-53).

The selection of the amount of the compound of Muller to add to the HSCs in the method of Waki would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Waki teach varying the amount of PDE4 inhibitor added to the cells (Figures 1-4). A holding of obviousness over the cited claims is therefore clearly required.

The selection of mammal from which to obtain HSCs would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing

that murine and human bone marrow have similar properties. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute varying amounts of the compound of Muller for the varying amounts of XT-44 and in the method of Waki et al. because the compounds are functional equivalents, and because the amount of compound would have constituted routine optimization at the time of the invention. Furthermore, substituting human HSCs for murine HSCs would have been obvious.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicants allege that Waki does not teach that XT-44 modulates differentiation of HSCs to blood cells (Reply, page 12, paragraph 1). These arguments have been fully considered, but they are not persuasive.

As discussed above, Gaspar Elsas established a link between PDE4 inhibition in stem cells and subsequent cAMP elevation and hematopoietic differentiation. Waki is relied upon as a teaching of administering a PDE4 inhibitor (a compound that has an activity linked by Gaspar Elsas to blood cell differentiation) to an animal *in vivo*. Whether Waki recognized the effect of XT-44 on hematopoiesis is not at issue here; the administration steps taught by the cited prior art is identical to the claimed steps.

M.P.E.P. § 2141.02 teaches, "'In determining whether the invention as a whole would have been obvious under 35 U.S.C. 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter

which is literally recited in the claim in question... but also to those properties of the subject matter which are inherent in the subject matter and are disclosed in the specification. . . Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim, it is this invention as a whole, and not some part of it, which must be obvious under 35 U.S.C. 103.' *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1977) (emphasis in original) (citations omitted). See also *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963), which indicates that "[f]rom the standpoint of patent law, a compound and all its properties are inseparable.' Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). In this case, a link between PDE4 inhibition and hematopoietic differentiation was known in the art (as taught by Gaspar Elsas), so the person of ordinary skill in the art would have expected that the *in vivo* administration of a PDE4 inhibitor as taught by Waki would have promoted differentiation to blood cells.

No claims are allowed. No claims are free of the art.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art

may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart